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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/088,139

12/17/2002

Anne Eckert

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EXAMINER

HAMA, JOANNE

ART UNIT

PAPER NUMBER

1632

NOTIFICATION DATE

DELIVERY MODE

05/07/2007

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatent.E-Filing@sanofi-aventis.com  
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**Office Action Summary**

Application No.

10/088,139

Applicant(s)

ECKERT ET AL.

Examiner

Joanne Hama, Ph.D.

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 21 February 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-8 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-8 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 21, 2007 has been entered.

Applicant indicates that in response to the Advisory Action of October 24, 2006, that in Applicant's October 3, 2006 reply that support for the claim amendments is found in the specification as filed, for example, in the original claims and at page 4, lines 4 and 5 and the last full sentence. Thus, the amendment to the claim is not new matter. In response, the Examiner has found the citation to not be new matter. However, it is noted that due to Applicant's amendment to claim 4, the wording has changed the types of mutations found in PS1 that the claims require a new search and consideration.

It is noted that in Applicant's Request for Continued Examination (RCE) Transmittal, February 21, 2007, that it was requested that the response filed after the Final Action be considered. Thus, the response and claim amendments filed October 3, 2006 are to be considered in this Office Action.

Claims 1, 3, 4 are amended.

Claims 1-8 are under consideration.

In the response filed by Applicant, October 3, 2006, Applicant indicates that finality of the Office Action should be withdrawn as the Office Action has been modified to apply to Alzheimer's disease (Applicant's response, page 3). In response, Applicant's response is moot as Applicant has filed an RCE.

**Withdrawn Rejection**

**35 U.S.C. § 112, 1<sup>st</sup> parag. Written Description**

Applicant's arguments, see page 6-7 of Applicant's response, filed October 3, 2006, with respect to the rejection of claims 1-8 have been fully considered. Upon further consideration, the rejection is withdrawn because the sequence of presenilin 1 (PS1) is known in the art and that the mutations (i.e. amino acid substitutions) associated with PS1 have been characterized (see also specification, page 5, 2<sup>nd</sup> parag.). The rejection of claims 1-8 has been withdrawn.

**35 U.S.C. § 112, 2<sup>nd</sup> parag.**

Applicant's arguments, see page 7 of Applicant's response, filed October 3, 2006, with respect to the rejection of claim 4 have been fully considered and are persuasive. Applicant has amended claim 4 such that the claim is in Markush format. The rejection of claim 4 has been withdrawn.

**New/Maintained Rejections**

**Claim Rejections - 35 USC § 101**

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35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-8 remain rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility, for reasons of record, July 14, 2005 and April 4, 2006.

Applicant's arguments filed October 3, 2006 have been fully considered but they are not persuasive.

Applicant indicates that the Office Action acknowledged that the transgenic mammalian animal model could be used to monitor apoptosis and that the Office Action asserted that correlation or relationship to a human disorder is not readily apparent. Applicant indicates that the Office Action continued its reasoning with, "a description of what a material does, rather than of what it is, usually does not suffice." Applicant indicates that this rejection is improper. Applicant indicates that the claimed invention relates to a transgenic animal expressing a multimutated form of presenilin 1 (PS1) and what the invention is capable of (or does) is also recited in the same independent claim. Since "what it is" is clearly recited in the claim, the citation of *Reagents of Univ. of Cal. V. Eli Lilly & Co., Inc.*, is improper (Applicant's response, page 3, under "Rejection under 35 U.S.C. § 101"). In response, this is not persuasive. As indicated in the Office Action, while it is understood that the specification teaches transgenic mice that express a multimutated form of PS1 and that these mice exhibit apoptosis in their T lymphocytes, the specification and the art provide no guidance what relationship multimutated PS1, apoptotic T lymphocytes, and Alzheimer's disease have to do with each other such that the claimed non-human mammals can be used. Indicating that the mice described in

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the specification have a particular phenotype does not provide guidance as to what use the mice have such that the claimed mice can be used as an animal model of disease or condition (e.g., here, apoptotic T lymphocytes). Subsequently, the claimed animal cannot then also then be used to screen for drugs that treat symptoms associated with Alzheimer's disease. Note that studying the process of apoptosis in the mice and using the mice to screen for compounds that, for example, inhibit apoptosis T lymphocytes, is not a specific and substantial use of the mice as nothing in the specification provides guidance that there is a biological relationship between multimutated PS-1, apoptotic T lymphocytes, and Alzheimer's disease. This issue will be further addressed in the Enablement rejection.

With regard to the Office Action indicating that the relationship between mutant PS1, apoptosis, and Alzheimer's disease was unclear and that the Office Action indicated that the mice described in the specification would need further characterization, Applicant indicates that this aspect of the rejection is improper as the claims do not recite Alzheimer's disease and thus assertions relating specifically to Alzheimer's disease are not understood. In response, the Examiner clarifies this issue. First, with regard to the Examiner indicating that the claimed mice require further characterization, the statement is based upon the fact that the specification provides no clear guidance that there is a relationship between multimutated PS1, apoptosis in T lymphocytes, and a human condition. Why this issue is important is discussed further in the Enablement rejection. To say that regardless of the relationship between multimutated PS1, apoptosis in T lymphocytes, and Alzheimer's disease, an artisan

could use the claimed animals to study apoptosis in T lymphocytes, is not a specific and substantial use of the claimed animals. This is because the mechanism by which apoptosis occurs in T lymphocytes in the claimed animals is different from that exhibited by other diseases or disorders, such as AIDS or a zinc deficiency, that the claimed animals cannot be a model for these diseases or disorders. For further discussion, see the Enablement rejection.

Applicant indicates that the rejection is improper because the claims do not recite Alzheimer's disease (Applicant's response, page 4, 1<sup>st</sup> parag.). In response, the claims broadly encompass any neurodegenerative disease, e.g. see claim 6, which Alzheimer's disease is one. Alzheimer's disease was of particular focus because the specification and the art teach that there is a relationship between PS1 and Alzheimer's disease. The rejection is maintained because neither the specification nor the art provide any guidance that the claimed animals are a model of Alzheimer's disease and the specification does not provide any other guidance as to what neurodegenerative disease the claimed animals have such that the method claims could be practiced. In particular for claims 6 and 8, the specification provides no guidance that the claimed mice exhibit any neurodegenerative disease such that the claimed methods could be practiced. As such, practicing the claimed method using the claimed animals and cells is not readily apparent.

Applicant indicates that Alzheimer's disease is but one disease known to involve an altered apoptotic etiology and that a real world association between the multimutated gene and monitoring apoptosis has been shown (Applicant's response, page 4, 1<sup>st</sup>

parag). In response, this is not persuasive because it is not entirely clear that expression of multimutated PS1 is responsible for the apoptosis in T lymphocytes. Note that the Enablement rejection indicates that post-filing art (Leutner et al.) teaches that PS1 with 5 mutations has severe structural alterations and that an artisan cannot predict whether the shape change in PS1 with 5 mutations necessarily triggered apoptosis in T lymphocytes. Note that the art teaches that it is equally likely that non-specific effects, such as genetic background can cause unrelated phenotypes to be exhibited by a transgenic animal (e.g. see Auerbach citation, below). As such, because it is unclear what causes the apoptosis in the claimed animals, an artisan would require further studies to determine whether the phenotypes are related to PS1 comprising 5 mutations and to determine what disease or disorder has the same pathology as that exhibited by the claimed animals, such that they can be used. As stated in the Guidelines of the Federal Register, Vol. 66, No. 4, pp. 1092-1099, research that involves studying the properties of the claimed product itself does not constitute a substantial utility.

Applicant also indicates that apoptosis is known to be a process important for growth and maintenance of animals and that malfunction of apoptotic pathways has been observed in many disease states, including neurodegenerative disease (Applicant's response, page 4, 1<sup>st</sup> parag.). In response, the specification teaches that apoptosis occurs in T lymphocytes and does not indicate that any neurological tissue in the transgenic mice underwent any apoptotic event. As such, to indicate a correlation between apoptosis and neurodegenerative disease, as they apply to the claimed invention, is not readily apparent. It is noted that post-filing art Leutner et al., 2000,

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Neuroscience Letters, 292: 87-90, also indicate that the mice expressing multmutated PS1 do not exhibit any neurological pathology, page 88, 1<sup>st</sup> col., 4<sup>th</sup> parag. (for further discussion, see Enablement). Thus, the method of using the claimed animals and the cells of the claimed animals in a method of detecting compounds for the treatment of neurodegenerative diseases (claims 6 and 8) are not readily apparent.

Applicant indicates that the Office Action acknowledges the showing in the specification that the animals of the instant invention exhibit increased sensitivity to apoptosis, such as found in Alzheimer's disease and thus, Applicant submit that this showing provides ample evidence of "real world" utility (Applicant's response, page 4, 2<sup>nd</sup> parag.). In response, indicating that the transgenic mice exhibit apoptosis in T lymphocytes does not demonstrate a "real world" utility of the claimed mice. As discussed above, it is unclear whether PS1 comprising 5 mutations triggered apoptosis in the claimed animals, and it is unclear what pathology the claimed animals exhibit such that they are models of T lymphocyte apoptosis in Alzheimer's disease.

Applicant indicates that the Office Action chose one indication of Alzheimer's disease, amyloid plaques, and asserts since animals were not sacrificed for the express purpose of observing plaques, that a relationship between Alzheimer's disease and PS1 was unclear. Applicant indicates that this is an improper standard and that it is improper for the Office to require that all possible manifestations of a disease state be proven in a model to show utility in monitoring a disease state (Applicant's response, page 4, 2<sup>nd</sup> parag.). In response, the Examiner questioned whether the mice described in the specification exhibited any amyloid plaques because the Examiner questioned

whether the claimed animals were models of human disease such that the claimed animals had specific and substantial utility. The most likely human disease to model for a transgenic mouse expressing mutant forms of PS1 is Alzheimer's disease as the art teaches that one protein involved in the etiology of Alzheimer's disease is PS1, e.g. see Marjaux et al., 2004, Neuron, 42: 189-192. The question of whether an animal model exhibits neuritic plaques arises because this is one definitive characteristic of Alzheimer's disease (e.g. see Wengenack et al., 2000, Nature Biotechnology, 18: 868-872, abstract). Given that the specification provides no guidance that the transgenic mice described in the specification exhibit any characteristics of Alzheimer's disease (e.g. neuritic plaques), the Examiner then needed to determine whether there was any Alzheimer's disease wherein the patient has multimutated PS1, does not exhibit any neuritic plaques, and exhibits apoptotic T lymphocytes, such that the claimed animals could be used. In addition to this, the Examiner considered whether the art or specification teaches that the mice described in the specification could be used to treat Alzheimer's disease via treatment of the T lymphocytes. No guidance was provided. Neither the art nor the specification provides guidance of Alzheimer's disease patients that fit these characteristics nor was there guidance as to how to use the claimed animals such that they are a model of disease. Failing that, the Examiner had to determine whether there was any specific and substantial use of the transgenic mice described in the specification, which exhibit apoptosis in T lymphocytes, such that the claimed mice could be used. As discussed above and in the Enablement rejection, the claimed animals are not models for apoptotic T lymphocytes. Applicant indicates that it

is improper for the Office to require that all possible manifestations of a disease state be proven in a model to show utility in monitoring a disease state. Applicant indicates that the fallacy of this requirement by noting that human Alzheimer's disease patients are frequently diagnosed without invasion biopsy of their brain tissue (Applicant's response, page 4, 2<sup>nd</sup> parag.). In response, this is not persuasive because post-filing art teaches that the only definitive diagnosis for Alzheimer's disease is postmortem observation of neuritic plaques and neurofibrillary tangles (Wengenack et al., abstract). Further, the art teaches that other neurodegenerative diseases, such as AIDS exhibit apoptosis in T lymphocytes (Bell and Dockrell, 2003, JEADV, 17: 178-183, abstract). However, apoptosis in T lymphocytes in AIDS patients have different etiology and pathology than that of the claimed mice. As such, because the specification does not provide guidance to use the claimed animal as a model of disease, the use of the claimed animals is not readily apparent. Because it is unclear how to use the claimed animal, the use of them in screens for compounds is not readily apparent as well.

Thus, the claims remain rejected.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 remain rejected in modified form under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains

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subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record, July 14, 2005 and April 4, 2006.

It is noted that new issues related to the rejections at hand are indicated as follows. Response to Applicant's rebuttals of October 3, 2006 will be provided after addressing these new issues.

While the specification teaches that transgenic multimutant presenilin 1 (PS1) mice were generated (specification, Example 1) and that the mice exhibited apoptosis in their T lymphocytes (specification, Example 2), the specification does not provide an enabling disclosure such that the mice can be readily used. One indication that it is not readily apparent how to use the mice described in the specification is that nothing in the specification teaches that the mice described in the specification exhibits any neurodegeneration, such that the claimed animals could be used (e.g. see claims 6 and 8). In particular, the specification does not provide guidance that the mice described in the specification exhibit any neurodegeneration associated with Alzheimer's disease. The Examiner focuses on neurodegeneration associated with Alzheimer's disease (versus any other neurodegenerative disorder) because the art indicates that one protein associated with the etiology of Alzheimer's disease is presenilin 1 (PS1), e.g. see Marjaux et al., 2004, Neuron, 42: 189-192. The specification does not provide guidance otherwise that overexpression of mutant PS1 is associated with any other neurodegenerative disorder. In addition to this issue, while the specification teaches that transgenic mice comprising the transgene construct that overexpress PS1

comprising 5 mutations exhibit apoptosis in their T lymphocytes, the specification does not provide guidance as to how treating apoptosis in T lymphocytes relates to treatment of neurodegenerative diseases. This issue becomes even less clear in light of the fact that the mice described in the specification are not described to have any neurodegeneration.

While it may be contemplated that the claimed animals could be used in a general method of treating disorders associated with apoptotic T lymphocytes, the art teaches that apoptosis in T lymphocytes have different etiologies and pathologies, wherein the etiology/pathology of the mice described in the specification could not be used to screen for medicaments to treat other apoptotic T lymphocyte conditions. For example, apoptosis in T lymphocytes can occur in HIV patients and in patients who have a zinc deficiency, and the art teaches that apoptosis in each disease or disorder is different. In the case of HIV, the art teaches T lymphocyte apoptosis is Fas-mediated (e.g. see Badley et al., 1996, Journal of Virology, 70: 199-206, abstract) and in the case of patients who have a zinc deficiency, increased levels of p57<sup>lck</sup> increases apoptosis in T lymphocytes (e.g. see LePage et al., 1998, The Journal of Nutrition, 129: 620-627, abstract). As such, because the specification and art provide no guidance between the relationship between multimutated PS1 and T lymphocyte apoptosis, the mouse described in the specification is not a model of a human condition and thus, the purported use of the mouse is not readily apparent.

Another indication that it is not readily apparent how to use the mice stems from the fact that the specification teaches that the multimutant PS1 protein, PS1M5, is not

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processed (i.e., cleaved) like wild type PS1 or PS1M146L (PS1 with one mutation) (specification, Example 1, page 22). This raises an issue because according to post-filing art, PS1M5 (a PS1 having the same 5 point mutations as that described in the specification), has severe structural alterations (Leutner et al., 2000, Neuroscience Letters, 292: 87-90; page 89, 1<sup>st</sup> col., 1<sup>st</sup> parag.) and because there are structural alterations, it is unclear what biological function (if any) PS1M5 has such that apoptosis occurs in T lymphocytes. Given that it is unclear what biological function PS1M5 has, an artisan cannot predict that PS1M5 effects the same pathology as that seen in T lymphocytes of Alzheimer's patients. As such, it is unclear that the mice described in the specification are models of apoptosis in T lymphocytes.

Applicant's arguments filed October 3, 2006 have been fully considered but they are not persuasive.

With regard to Applicant addressing the rejection as it relates to providing guidance between a biological relationship between apoptosis, Alzheimer's disease, and mutant PS1, Applicant indicates that the specification, page 6, 2<sup>nd</sup> parag., indicates that the results described in the examples demonstrate the relationship between multimutated PS1, an increased sensitivity, and Alzheimer's disease (Applicant's response, page 5, 1<sup>st</sup>-2<sup>nd</sup> parag.). In response, while Applicant provides this citation, this is not persuasive because the citation in the specification is an assertion and not evidence. It is noted that while the specification teaches that transgenic mice exhibit apoptotic T lymphocytes, an artisan cannot reasonably predict that expression of any transgene in a transgenic animal necessarily means that the phenotype exhibited by the

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animal is related to the transgene. First, as indicated above, Leutner et al., indicates that PS1M5 has a severely altered structure. As such, it is not entirely clear what, if any, biological activity PS1M5 has in the claimed animals such that an artisan could reasonably predict that expression of PS1M5 resulted in apoptotic T lymphocytes.

Second, the art indicates that an artisan cannot reasonably predict that the phenotype exhibited by the transgenic animal is necessarily related to the transgene. Note for example that Auerbach, 2004, *Acta Biochimica Polonica*, 51: 9-31 teaches that unexpected phenotypes in transgenic animals can result from an insertional mutation and/or from differences in genetic backgrounds of the animals (Auerbach, page 24, under "Final Comments"). As such, because the art indicates these issues of unpredictability, an artisan cannot reasonably predict that the mice described in the specification has a phenotype necessarily related to transgene overexpression, nor can an artisan reasonably then predict that the mice described in the specification necessarily be a model of apoptotic T lymphocytes related to Alzheimer's disease.

With regard to the issue of enablement as it applies to the breadth of promoters and breadth of animals claimed, Applicant indicates that the claims have been amended to "mammalian" (Applicant's response, page 5, 3<sup>rd</sup> parag.). In response, this is not persuasive. According to the art, an artisan cannot reasonably predict that the components that comprise the transgene construct necessarily work in various species of animals. As indicated in the Office Action, July 14, 2005, page 8, Hammer et al., 1990, teach while a particular transgene construct in rats could recapitulate a human disease, the same transgene construct could not in mice. In the case of promoters, the

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art teaches that not all promoters have predictable activity in heterologous animals.

Cowan et al. 2003, Xenotransplantation, 10: 223-231 teach that promoters of three human genes, ICAM-2, hCRPs, and PECAM-1, are predominantly expressed in vascular endothelium in mice and pigs. When tissue specific expression was measured, it was found that while mice showed a distinct expression profile of the three human genes, the tissue expression profiles of the three human gene promoters were distinctly different in pigs. The authors concluded that "promoter performance in mice and pigs was not equivalent," and that "the weak expression driven by the human ICAM-2 promoter in pigs relative to mice suggests the need for additional regulatory elements to achieve species-specific gene expression in pigs (Cowan et al., abstract)."

In the case of expressing heterologous genes of interest, the art teaches that proteins encoded by an artisan's gene of interest do not always behave in a predictable manner in heterologous non-human animals. For example, Hammer et al. 1986, J. of Anim. Sci., 63: 269-278 teach that while transgenic mice that overexpressed human growth hormone exhibited enhanced growth, transgenic pigs that expressed human growth hormone did not increase weight gain (Hammer et al., page 276, under "Effect of Foreign GH on Growth"). According to the art, the unpredictability in using heterologous proteins in transgenic animals stem from difference in the species with regard to genetic background, gene expression, metabolism, and signal transduction, Racay, 2002, Bratisl Lek Listy, 103: 121-126; page 124, 2<sup>nd</sup> col. under point 5. As these issues apply the instant invention, while the specification provides an example of a transgenic mouse comprising a transgene construct comprising a nucleic acid sequence encoding PS1

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comprising 5 particular point mutations, the specification does not provide guidance to address the issues in the art such that an artisan is enabled for the full breadth of the claimed invention, particularly with regard to animal species of presenilin, and promoter to be used to drive expression in renewable peripheral tissue (more specifically T lymphocytes). Thus, the claims remain rejected.

With regard to the Office Action, April 4, 2006, page 7, indicating that the effect seen in the transgenic mouse described in the specification may be due to inactivation of a gene at an insertion site or that some unforeseen unpredictable event might mitigate operation of the transgenic model, Applicant indicates that experience has shown that the transgenic model is repeatable and refers to the specification, page 3, line 12, where multiple examples of successful transgenic production are described. In response, the Examiner looked at page 3 and has found nothing indicating multiple examples of successful repeatable transgenic production of the claimed animals. As discussed above, it is unclear without further guidance that the mice described in the specification necessarily exhibit apoptotic lymphocytes because of the transgene or because of unrelated factors (e.g. genetic background and/or the PS1M5 inducing non-specific biological activity) which result in mice that exhibit this particular phenotype.

With regard to the aspect of renewable tissue, Applicant indicates that inoperative embodiments are enabled (Applicant's response, page 5). In response, applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 38 USPQ 189 (CCPA 1938). In cases involving

unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." As such, while the specification teaches T lymphocytes, the specification does not teach how to arrive at apoptosis in other renewable peripheral tissue such as blood. Thus, the claims remain rejected.

Applicant addresses the rejection provided on pages 8-9 of the Office Action, wherein the Office Action discussed the scope of the claims as they relate to "neurodegenerative diseases." Applicant indicates that page 6 of the specification provide guidance to counter the assertion of the Office Action. Applicant indicates that the specification is replete with associations between the model and Alzheimer's disease (Applicant's response, page 6, 2<sup>nd</sup>-3<sup>rd</sup> parag.). In response, while Applicant indicates this citation of the specification, it is not persuasive because asserting a relationship between PS1 comprising 5 mutations and Alzheimer's disease is not

evidence that PS1 comprising 5 mutations causes Alzheimer's disease such that the claimed animals are enabled. As described above, it is unclear whether PS1 comprising 5 mutations has any activity that contributes to Alzheimer's disease because the specification does not provide guidance that the protein recapitulates symptoms associated with the disease, such as neuritic plaques. In addition to this issue, post-filing art teaches that PS1M5 has a severely altered structure that it is unclear whether PS1M5 has any activity related to the pathology of Alzheimer's disease or because it has a new structure and has adopted a new function which triggers a phenotype unrelated to Alzheimer's disease. Because the mice described in the Examples do not have phenotypes that indicate that they are models of Alzheimer's disease, an artisan cannot reasonably predict that the mice can be used as a model of the disease. To indicate that the mice described in the specification is a model of disease because it overexpresses a protein involved in the etiology of the disease is not sufficient, for the reasons described above. Thus, the claims remain rejected.

Thus, the claims remain rejected.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 7, 8 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5, 7 are missing articles, "a," "an," or "the," that start the sentence.

Claim 8 recites the limitation "said cell" in claim 1-5. There is insufficient antecedent basis for this limitation in the claim.

### ***Conclusion***

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

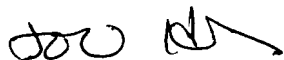
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Joanne Hama

AU 1632

A handwritten signature in black ink, appearing to read 'Joanne Hama', with a stylized flourish extending to the right.